Eur J Vasc Endovasc Surg (2009) **37**, 311–318

Perioperative Red Blood Cell Transfusion and Outcome in Stable Patients after Elective Major Vascular Surgery

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Submitted 3 October 2008; accepted 3 December 2008
Available online 25 December 2008

KEYWORDS
Anaemia;
Transfusion;
Vascular surgery;
Outcome;
Myocardial infarction;
Death

Abstract *Objectives:* Definitive evidence that red blood cell transfusion improves outcome after vascular surgery is lacking. The aims of the study were to determine, among stable consecutive patients who underwent elective major vascular surgery, (1) the association between postoperative transfusion and 30-day death, myocardial infarction, and both, and (2) and if this association differs according to the presence of postoperative anaemia (haemoglobin value less than 9.0 g/dL within 7 days after surgery).
Methods: A retrospective observational study was conducted on 359 patients prospectively screened according to the ACC/AHA guidelines for preoperative risk in non-cardiac surgery. Main outcome was 30-day death; secondary outcomes 30-day myocardial infarction, and composite of 30-day myocardial infarction or death.
Results: Of the patients included, 95 (26.5%) received at least one unit of red blood cells. Patients who received transfusion had a significantly increased hazard of 30-day death (hazard ratio [HR] 11.72, 95% confidence interval [CI] 3.92–35.10; $p < 0.0001$), myocardial infarction (HR 3.3, 95% CI 1.7–6.1; $p = 0.0003$), and both (HR 4.0 95% CI 2.2–7.3; $p < 0.0001$). Such associations held even after adjusting for baseline characteristics, surgical risk, bleeding, and propensity to receive transfusion. There was a significant interaction between transfusion and postoperative anaemia ($p = 0.012$). In patients without anaemia, transfusion was

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doi:10.1016/j.ejvs.2008.12.002

associated with higher risk of 30-day death (HR 19.20, 95% CI 3.99–92.45; $p = 0.007$), myocardial infarction (HR 5.05, 95% CI 2.23–11.44; $p = 0.0001$), and both. Conversely, in patients with anaemia this association was not significant.
Conclusions: In patients who underwent elective major vascular surgery, perioperative transfusion was associated with a significantly increased risk of 30-day events which was more attributable to patients with lesser degree of anaemia. Our data caution against the use of liberal transfusion in stable vascular surgery patients.

Introduction

Anaemia occurs frequently after vascular surgery[1] and usually results in red blood cell transfusion (RBT).[2] Allogenic RBT is a finite[3] and expensive[4] resource, and its use can be associated with a risk for infection and transfusion reactions.[5] Thus, there has been concern that if transfusion policies are too liberal, they could result in excess morbidity and mortality.[6] Although these risks are well reported and have led to a re-evaluation of the criteria for the use of blood products,[5] a significant proportion of practitioners have not modified their approach because of fear of the mortality and morbidity related to anaemia, especially in patients with coronary artery disease.[7] It is clear that anaemia is less tolerated in older patients[8] and in patients with coronary disease[3,9] undergoing coronary artery bypass graft surgery.[10] Although RBT should increase tissue oxygenation in patients with coronary artery disease,[11] the data concerning the effectiveness of this approach are controversial.[6,12,13] This risk–benefit relationship is of particular importance in patients who undergo major vascular surgical procedures. Thus, whether these putative benefits are greater than the risks associated with RBT in anaemic stable patients during vascular surgery is not known. Accordingly, the aims of this study were to assess, among consecutive stable patients who underwent major vascular surgery, (1) the association between RBT and events through 30 days, including death, myocardial infarction, and the composite of death or myocardial infarction, and (2) to assess if the association between RBT and events differs in relation to the severity of the anaemia.

Methods

We studied 359 consecutive patients who were admitted to our Institution for elective major vascular surgery. Before surgery all patients were prospectively screened according to the ACC/AHA guidelines for preoperative evaluation of cardiac risk in non-cardiac surgery[14] as previously described by our group.[15] We included only patients referred for elective open vascular surgery who could not be unstable or have major clinical cardiovascular risk predictors (unstable coronary syndromes, decompensated heart failure, significant arrhythmias, and severe valve disease). Data were provided by review of hospital charts, which was assessed by two independent investigators (L.P. and T.G.). We excluded patients who had haemorrhagic hypovolaemic shock requiring emergency RBT.

Baseline characteristics

Diabetes mellitus, hypertension, smoking, hyperlipidaemia, chronic obstructive pulmonary disease, chronic renal insufficiency, history of coronary artery disease, and history of chronic heart failure were defined on the basis of clinician diagnosis according to contemporary guidelines.

Type of surgery was classified on the basis of level of surgery-specific risk according to ACC/AHA guidelines (intermediate risk: carotid surgery; high risk: aortic surgery and peripheral surgery).

Anaemia, bleeding, and blood transfusion

Anaemia was used as the exposure variable and was defined as a haemoglobin value less than 9.0 g/dL within 7 days after surgery. Severely anaemic patients (haemoglobin <7.0 g/dL) were excluded from the study. These thresholds were defined in keeping with the Transfusion Requirements in Critical Care (TRICC) trial[16] and subsequent expert recommendations[17] suggesting that, in the absence of acute bleeding, haemoglobin levels of 7.0–9.0 g/dL are well tolerated by most critically ill patients and that a transfusion threshold of 7.0 g/dL is appropriate. The lowest postoperative haemoglobin level prior to the first transfusion or, for the non-transfused patients, the lowest haemoglobin level during this time period were used to categorize anaemia. Haemoglobin was measured before surgery, soon after surgery and every 24 h for 7 days, and when clinically indicated. We used haemoglobin level because of the poor predictive value of haematocrit for erythrocyte deficits after extensive elective vascular operations.[18]

Postoperative bleeding severity was defined according to the Thrombolysis In Myocardial Infarction (TIMI) study classification. Minor bleeding was defined as haemoglobin decrease of 3 g/dL or less, major bleeding as haemoglobin decrease of 5 g/dL or more.[19]

Postoperative RBT was defined as a transfusion occurring within 7 days after vascular surgery, and was determined at the discretion of each patient's physician. There was no haemoglobin level that mandated RBT. Data on the number of units transfused, as well as the date and type or blood product used, were recorded for each patient. At our institution information on transfusion is accurately documented as per national and institutional guidelines; monitoring and quality control for RBT practice are in place, and all patients gave written informed consent for transfusion.

Definition of events

Follow-up was provided by review of hospital charts, telephone interview, death certificates, and autopsy reports (if available), which were assessed by two independent investigators who were unaware of the patients' history, laboratory examinations, and aim of the study (A.M. and A.D.G.). The main dependent variable was death through 30 days; secondary endpoints were myocardial infarction through 30 days, and the composite endpoint death or myocardial infarction through 30 days. Myocardial infarction was clinically and independently diagnosed by pre-specified criteria using the new American College of Cardiology/European Society of Cardiology (ACC/ESC) definition which requires a typical rise and gradual fall of troponin values when either the setting, clinical or electrocardiographic findings suggest the presence of acute ischaemia.[20] In case of disagreement, the matter was solved by consensus. Cardiac troponin I was measured with the Stratus CS STAT Fluorimetric Analyzer (Dade Behring Inc., Newark, DE) on the first, second and third postoperative day in all patients regardless of clinical setting as previously described.[15] During follow-up cardiac troponin I measurements were left to the discretion of the treating physician but in most cases, values were obtained if there were signs or symptoms suggestive of ischaemia. The minimum detectable concentration is with the Dade CS assay is 0.03 ng/mL and the upper reference limit (99th percentile of the reference range) is 0.07 ng/mL. At the time of this study in our institute, the lowest concentration with coefficient of variation $<10\%$ was 0.10 ng/mL and this level of increase was used to define troponin elevations.

Statistical analysis

Baseline characteristics were compared across groups using χ^2 tests for categorical variables or Fisher's exact test, whereas the *t*-test was used to compare continuous variables; variables with highly skewed distribution were compared by the Mann–Whitney non-parametric test. Logistic regression models were used to identify the baseline predictors of postoperative RBT and to calculate the propensity to receive transfusion. This propensity score was used as a covariate for multivariable adjustment. The predicted probability for transfusion was calculated using the following variables: age, sex, high-risk surgery, diabetes mellitus, hypertension, smoking, hyperlipidaemia, previous coronary disease, chronic heart failure, renal insufficiency, chronic obstructive pulmonary disease, and bleeding.

The predicted probability for the risk of death was calculated using the following variables: age, sex, diabetes mellitus, hypertension, smoking, hyperlipidaemia, previous coronary disease, chronic heart failure, renal insufficiency, chronic obstructive pulmonary disease, high-risk surgery, perioperative beta-blockers, bleeding, postoperative anaemia, and preoperative haemoglobin. This propensity score then was used for further multivariable adjustment given there were differences in some medical co-variants associated with increased risk.

Kaplan–Meier analysis was used to show 30-day mortality among patients who did and did not receive RBT; the log-rank test was used to compare the two groups. Cox proportional hazard regression models were used to examine the unadjusted and adjusted hazard ratio (HR) and 95% confidence interval (CI) for events through 30 days among patients who received RBT compared to those who did not receive RBT (referent). By using this model, patients who were transfused after the occurrence of the event were classified as not transfused. Because the exposure to RBT was not random, several multivariable models were created in order to account for potential confounders including confounding by indication. The first model incorporated preoperative data (we included variables with $p < 0.10$ at univariate analysis and age and gender were forced into the model); the second was adjusted for age, sex, surgical risk, and bleeding; the third model was adjusted for the propensity to undergo transfusion; and finally in a last model we adjusted for the overall propensity score for death.

The interactions of RBT and anaemia, RBT and bleeding, and RBT and history of coronary artery disease were tested in the Cox models and multivariable adjustments for propensity scores were performed. All tests were two-sided, and for all analyses, $p < 0.05$ was considered statistically significant. Analyses were carried out by using software SPSS® version 11.0 for Windows (SPSS Institute Inc., Chicago, IL, USA) and STATA® version 8.0 (College Station, TX, USA).

Results

Three hundred and fifty-nine patients (mean age 70.0 ± 9.1 years, 96 [26.7%] women) were included in the study; 158 (44.0%) underwent intermediate risk vascular surgery (carotid surgery) and 201 (56.0%) high risk vascular surgery (150 infra-inguinal and 51 aortic surgery).

Blood transfusion

Of study patients, 95 (26.5%) received at least one unit of red blood cells, 65 (18.1%) patients received RBT intraoperatively, 62 (17.3%) after surgery, and 32 (8.9%) at both times. Compared with those who did not receive blood, patients who received a RBT had more medical comorbidities at presentation, especially chronic heart failure and chronic renal insufficiency. Furthermore, patients who received RBT were more likely to have undergone high-risk surgery. Particularly, among transfused patients carotid surgery was performed in 4.2% of cases, infra-inguinal intervention in 60.0% and aortic surgery in 35.8%; among non-transfused patients carotid surgery was performed in 58.3% of cases, infra-inguinal intervention in 35.2% and aortic surgery in 6.4% ($p < 0.001$). High-risk surgery had more postoperative bleeding and lower postoperative haemoglobin values. Only two patients had postoperative haemoglobin <7 g/dL and were not included in the study. About 53% of patients who underwent RBT were classified as having anaemia vs. 9% of those who did not receive RBT ($p < 0.001$). (Table 1) The mean number of units transfused was 3.3 ± 2.3 (range 1–16). Patients who underwent RBT

Table 1 Characteristics and odds ratios of patients who did, compared to those who did not (referent) receive RBT

Characteristics	No transfusion ($N = 264$)	Transfusion ($N = 95$)	OR (95% CI)	p
Mean age ± SD	69.9 ± 9.0	70.2 ± 9.6	1.00 (0.98–1.03)	0.795
Women (%)	69 (26.1)	27 (28.4)	1.12 (0.66–1.89)	0.666
Pre-operative data				
Diabetes mellitus (%)	96 (36.4)	41 (43.2)	1.33 (0.82–2.14)	0.243
Hypertension (%)	202 (76.5)	73 (76.8)	1.02 (0.58–1.78)	0.949
Smoking (%)	146 (55.3)	53 (55.8)	1.02 (0.64–1.63)	0.935
Hyperlipidaemia (%)	56 (21.2)	14 (14.7)	0.64 (0.34–1.22)	0.174
History of coronary disease (%)	74 (28.0)	22 (23.2)	1.45 (0.77–1.34)	0.358
Prior chronic heart failure (%)	51 (19.3)	28 (29.5)	1.74 (1.02–2.99)	0.042
Chronic renal insufficiency (%)	42 (15.9)	37 (38.9)	3.37 (1.99–5.72)	<0.0001
Chronic obstructive lung disease (%)	68 (25.8)	31 (32.6)	1.40 (0.84–2.32)	0.200
Intra-operative and postoperative data				
High-risk surgery (%)	110 (41.7)	91 (95.8)	3.17 (2.23–4.43)	<0.0001
Perioperative beta-blockers	163 (61.7)	44 (46.3)	0.53 (0.33–0.85)	0.010
Minor or major bleeding vs. no bleeding	26 (9.8)	51 (53.7)	10.6 (6.00–18.79)	<0.0001
Major bleeding	4 (1.5)	8 (8.6)	–	–
Mean lowest postoperative haemoglobin, g/dL ± SD	11.5 ± 1.7	9.2 ± 1.7	0.48 (0.40–0.57)	<0.0001
Postoperative anaemia (%)	25 (9.5)	50 (52.6)	10.62 (5.97–18.90)	<0.0001
Number of total blood unit transfused, median (25th–75th percentile)	–	3 (2–4)	–	–
Length of hospital stay (days), median (25th–75th percentile)	5 (4–9)	12 (9–18)	1.14 (1.10–1.19)	<0.0001
Admission to ICU (%)	20 (7.6)	40 (42.1)	8.87 (4.81–16.35)	<0.0001
Length of stay in ICU (days), median (25th–75th percentile)	1 (1–2)	1 (1–5)	1.35 (0.93–1.94)	0.085

OR, odds ratio; CI, confidence interval; ICU, intensive care unit.

had a prolonged length of hospital stay compared to those who did not undergo RBT and were more likely to require admission to an intensive care unit (all $p < 0.001$).

Blood transfusion and events

RBT was associated with a significantly increased risk of 30-day events. Fig. 1 shows the Kaplan–Meier curves for 30-day cumulative incidence of death among patients who did and did not receive RBT. Patients who received RBT had a higher risk of death than patients who did not receive RBT (log-rank $p < 0.0001$).

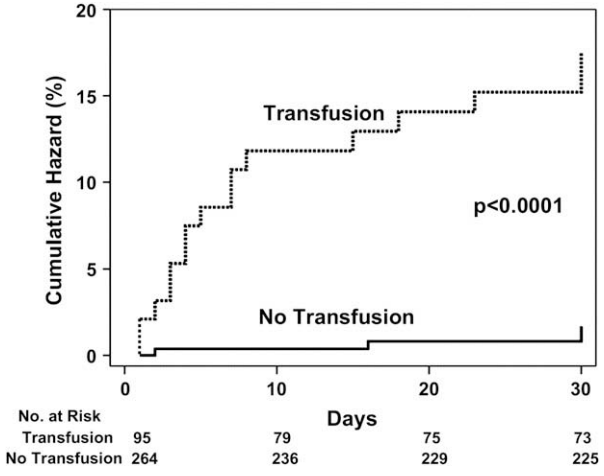

Figure 1 Kaplan–Meier cumulative incidence of 30-day death among patients who did and did not receive RBT.

At 30 days 20 had patients died, and 38 experienced acute myocardial infarction. Compared with patients who did not undergo RBT, patients who received RBT had a significantly increased hazard for 30-day death (HR 11.72, 95% CI 3.92–35.10; $p < 0.0001$), myocardial infarction (HR 3.32, 95% CI 1.75–6.27; $p = 0.0003$), and for the composite endpoint of myocardial infarction or death (HR 4.02 95% CI 2.23–7.27; $p < 0.0001$). These associations remained even after adjusting for relevant preoperative characteristics including age, gender, chronic heart failure, and chronic renal insufficiency (Table 2). The strong association between RBT and 30-day outcomes persisted after adjusting for high-risk surgery and bleeding (HR 7.81, 95% CI 2.32–26.32; $p = 0.001$ for death; HR 3.14, 95% CI 1.41–7.01; $p = 0.005$ for myocardial infarction; HR 3.98, 95% CI 1.91–8.27; $p = 0.0002$ for the composite of death or myocardial infarction). Similar results were obtained after adjusting for preoperative haemoglobin and intensive care unit (ICU) stay.

In order to account for other possible confounders we calculated the propensity to receive RBT with logistic regression. After adjusting for the propensity to undergo transfusion, patients who received RBT remained at higher risk of 30-day death compared to those who did not receive RBT (Table 2). A final propensity score for death was

Table 2 Frequency of 30-day events and unadjusted and adjusted hazard ratios for events through 30 days among patients who did compared to those who did not (referent) receive RBT

Outcomes	No transfusion ($N = 264$)	Transfusion ($N = 95$)	p	Unadjusted HR (95% CI)	Adjusted[a] HR (95% CI)	Adjusted[b] HR (95% CI)
				p	p	p
30-Day events (%)						
Death	4 (1.5%)	16 (16.8%)	<0.0001	11.72 (3.92—35.10) <0.0001	7.30 (2.39—22.28) 0.0004	5.38 (1.45—20.0) 0.012
Myocardial infarction	18 (6.8%)	20 (21.1%)	0.0001	3.32 (1.75—6.27) <0.0001	2.19 1.13—4.26 0.021	2.23 (0.98—5.09) 0.056
Myocardial infarction or death	19 (7.2%)	26 (27.4%)	<0.0001	4.02 (2.23—7.27) <0.0001	2.76 (1.49—5.12) 0.001	3.07 (1.43—6.59) 0.004

HR, hazard ratio.
[a] Adjusted for relevant preoperative characteristics: age, gender, chronic heart failure, and chronic renal insufficiency.
[b] Adjusted for transfusion propensity. The predicted probability for transfusion was calculated using the following variables: age, sex, surgery risk, diabetes, hypercholesterolaemia, smoking, hypertension, hyperlipidaemia, previous coronary disease, chronic heart failure, renal insufficiency, chronic obstructive pulmonary disease, and bleeding.

calculated incorporating all preoperative and intraoperative data and the strong association between RBT and 30-day death remained significant after adjustment for this propensity score (HR 5.45, 95% CI 1.77—18.00; $p = 0.003$).

There was a significant association between the number of units of packed red cells transfused and 30-day death (HR 1.31, 95% CI 1.20 to1.41; $p = 0.014$), myocardial infarction (HR 1.26, 95% CI 1.16—1.36; $p = 0.017$), and the composite endpoint of death or myocardial infarction (HR 1.26, 95% CI 1.18—1.78; $p = 0.010$). No significant interaction was detected between RBT and bleeding and between RBT and history of coronary disease in predicting events.

Transfusion occurred on average 1.0 ± 2.0 days after surgery. Only five patients had postoperative troponin elevation before receiving transfusion, exclusion of these patients from the analysis did not change the results.

The increased risk of death, myocardial infarction, and the composite endpoint myocardial infarction or death was maintained in the long term. After a mean follow-up of 16.3 ± 9.0 months HR was 4.02, 95% CI 2.24—7.87, $p < 0.001$ for death; HR 2.02, 95% CI 1.15—3.57, $p = 0.015$ for myocardial infarction; HR 2.67, 95% CI 1.71—4.18, $p < 0.001$ for the composite endpoint death or myocardial infarction.

Transfusion and postoperative anaemia

There was a significant interaction between RBT and postoperative anaemia ($p < 0.01$). Therefore, we stratified the patients according to the presence or absence of anaemia (Table 3). Among study patients 75 (20.9%) had anaemia. Among patients without anaemia, those who received RBT were more likely to have renal failure, to have undergone high-risk surgery, to have developed postoperative bleeding, and less likely to receive perioperative beta-blockers (all $p < 0.05$). Among patients with anaemia, transfused patients were more likely to have undergone high-risk surgery and to have developed postoperative bleeding, but did not differ significantly for other characteristics.

In patients without anaemia, RBT was associated with an almost 20-fold increased risk of 30-day death (HR 19.20, 95% CI 3.99—92.45; $p = 0.007$) and a five-fold increased risk of the composite of death or myocardial infarction (HR 5.05, 95% CI 2.23—11.44; $p = 0.0001$). Conversely, in patients with anaemia, there was no significant association between RBT and 30-day events (Table 4). In multivariable propensity score analyses, after adjusting for the predicted probability to undergo RBT the relation between RBT and 30 days events did not change. Indeed, patients without anaemia had a significantly increased risk of 30-day death, myocardial infarction, and the composite of death or myocardial infarction (Table 3). After adjusting for the predicted probability for death, RBT remained significantly associated with an increased risk of 30-day death (HR 11.59, 95% CI 2.29—58.73; $p = 0.003$) and death or myocardial infarction (HR 3.80, 95% CI 1.58—9.18; $p = 0.003$) among patients without anaemia, but not among patients with anaemia (HR 1.07, 95% CI 0.21—5.45; $p = 0.936$, and HR 0.66, 95% CI 0.25—1.73; $p = 0.400$, respectively).

Discussion

The present study suggests that, in elective major vascular surgery, perioperative RBT is associated with a significantly increased risk of 30-day death, myocardial infarction, and the composite of death or myocardial infarction among non-anaemic clinically stable patients preoperatively risk-stratified and treated according to the ACC/AHA guidelines for non-cardiac surgery. This association was independent of baseline characteristics, surgical risk, bleeding, presence of anaemia, and propensity to receive transfusion. Patients who received RBT had a significantly longer hospital stay. In contrast, our data indicate no association between RBT and events through 30 days among anaemic subjects. These data suggest caution against the use of RBT in stable patients with higher levels of postoperative haemoglobin.

Postoperative anaemia is a frequent complication of vascular surgery and it is associated with a significantly

Table 3 Baseline characteristics among patients who did and did not receive RBT by anemia

Baseline characteristics	No anaemia (haemoglobin ≥9 g/dL) ($N = 284$)			Anaemia (haemoglobin <9 g/dL) ($N = 75$)		
	No transfusion ($N = 239$)	Transfusion ($N = 45$)	*p*	No transfusion ($N = 25$)	Transfusion ($N = 50$)	*p*
Mean age ± SD	70.0 ± 9.1	70.2 ± 9.1	0.837	70.1 ± 9.7	69.0 ± 9.9	0.716
Women (%)	60 (25.1)	8 (17.8)	0.291	9 (36.0)	19 (38.0)	0.866
Pre-operative data						
Diabetes mellitus (%)	88 (36.8)	13 (28.9)	0.308	8 (32.0)	28 (56.0)	0.051
Hypertension (%)	185 (77.4)	32 (71.1)	0.362	17 (68.0)	41 (82.0)	0.172
Smoking (%)	134 (56.1)	26 (57.8)	0.832	12 (48.0)	27 (54.0)	0.624
Hyperlipidaemia (%)	48 (20.1)	6 (13.3)	0.290	8 (32.0)	8 (16.0)	0.111
History of coronary disease (%)	68 (28.5)	9 (20.0)	0.242	6 (24.0)	13 (26.0)	0.851
Prior chronic heart failure (%)	45 (18.8)	11 (24.4)	0.385	6 (24.0)	17 (34.0)	0.861
Chronic renal insufficiency (%)	36 (15.1)	14 (31.1)	0.010	6 (24.0)	23 (46.0)	0.065
Chronic obstructive pulmonary disease (%)	61 (25.5)	14 (31.1)	0.435	7 (28.0)	17 (34.0)	0.600
Intra-operative and postoperative data						
High-risk surgery (%)	99 (41.4)	44 (97.8)	<0.0001	11 (44.0)	47 (94.0)	<0.0001
Perioperative beta-blockers (%)	150 (62.8)	20 (44.4)	0.021	13 (52.0)	24 (48.0)	0.744
Bleeding (%)	21 (8.8)	17 (37.8)	<0.0001	5 (20.0)	34 (68.0)	<0.0001

increased risk of cardiac morbidity.[1] The usual treatment is RBT.[2,21] Indeed, patients undergoing vascular surgery are at risk for the adverse consequences of anaemia because of the high prevalence of underlying coronary disease.[22] Anaemic patients with coronary disease are at increased risk[3] because the compensatory mechanisms to anaemia may be impaired, resulting in risk of oxygen deprivation to vital organs.[9] However, although previous observational studies have suggested that vascular surgery patients are less tolerant to anaemia,[1] there is a lack of evidence to indicate that RBT improves outcomes in this population.[6] Our study demonstrates that RBT after major vascular surgery is associated with an increased hazard for 30-day death and acute myocardial infarction when used in patients who are not anaemic. Such an association held even after adjustment for the influence of several variables, including preoperative characteristics, surgical risk, postoperative bleeding, anaemia, and the propensity for RBT. The consistency of our findings through different outcomes and with multiple levels of adjustments underscores the robustness of our results. Our findings fully support and extend to vascular surgery patients the conclusion by the Anemia and Blood Transfusion in the Critically Ill (CRIT)[23] and the Anemia and Blood Transfusion in Critical Care (ABC)[24] studies. In these prospective, multicentre, cohort studies of intensive care unit patients, allogenic RBT were independently associated with mortality particularly when more than 2 red blood cell units were

Table 4 Hazard ratio for events through 30 days for patients who did compared to those who did not undergo RBT (referent) stratified by the presence of anaemia

	No anaemia ($N = 284$)			Anaemia ($N = 75$)		
	No transfusion ($N = 239$)	Transfusion ($N = 45$)		No transfusion ($N = 25$)	Transfusion ($N = 50$)	
	HR (referent)	HR (95% CI)	Adjusted[a] HR (95% CI)	HR (referent)	HR (95% CI)	Adjusted[a] HR (95% CI)
		p	*p*		*p*	*p*
30-Day death	1	19.20 (3.99—92.45) 0.007	18.7 (3.12—112.1) 0.001	1	2.35 (0.51—10.88) 0.274	0.64 (0.13—3.18) 0.642
30-Day myocardial infarction	1	3.49 (1.35—9.00) 0.010	2.66 (0.86—8.24) 0.089	1	0.92 (0.36—2.29) 0.851	0.78 (0.24—2.58) 0.228
30-Day myocardial infarction or death	1	5.05 (2.23—11.44) 0.0001	4.53 (1.69—12.12) 0.003	1	1.06 (0.43—2.59) 0.904	0.83 (0.26—2.60) 0.745

[a] Adjusted for the propensity to undergo transfusion.

transfused. More recently Rao et al.[25] demonstrated in the setting of acute coronary syndromes that 30-day mortality was almost 4 times higher in patients who did compared with those who did not undergo RBT.

It may be that RBT does not augment oxygen delivery[26,27] or that RBT units during preparation and storage undergo changes that contribute to decrease tissue oxygen delivery.[28,29] Moreover, the overall benefits of RBT are related to patients' capacity to compensate for anaemia which may already be adequate in patients with higher haemoglobin levels. In our study the association between RBT and events appeared to be independent of the presence of clinically detectable history of coronary disease.

These findings are in agreement with recent observations. Rao et al. reported that the increased risk of death after RBT in patients with acute coronary syndrome occurred especially among patients with a higher haematocrit level.[25] Bush et al.[30] preoperatively randomized 99 patients undergoing elective aortic and infrainguinal surgery to receive either a liberal transfusion strategy (maintaining a haemoglobin level of 10.0 g/dL) or a restrictive strategy (transfusion only for haemoglobin level $\leq$7.0 g/dL). In an intention-to treat analysis, there was no difference in myocardial ischaemia, myocardial infarction, or death between the strategies.

The mechanism whereby RBT worsens outcome in vascular surgery patients is beyond the scope of this study. RBT may have a number of unexpected consequences including activation of inflammatory pathways,[31] infection,[6] vasoconstriction, and platelet aggregation.[32] Of interest, our patients were likely to have diffuse distal coronary disease given the high prevalence of diabetes, hypertension, and chronic renal insufficiency. In these patients the prothrombotic properties of RBT may be enhanced[33] and thus RBT may actually impair oxygen delivery in some patients and induce myocardial ischemia.[25]

For patients with haemoglobin values $>$9 g/dL, the approach should focus on implementing blood conservation strategies, reducing perioperative blood loss, and improving fluid management, and by identifying optimal targets for transfusion triggers.[34,35] For patients who are more anaemic, it may well be that with larger data sets, RBT might be found to be of benefit but even in this subset, from our data, it appears that there are likely contrasting risks that should result in cautious RBT and a reliance on the other measures suggested above as well whenever possible.

Limitations

Our study was a retrospective analysis of consecutive stable patients undergoing elective major vascular surgery who had been prospectively risk stratified at one centre. However, it is challenging to perform a trial whereby subjects are randomly assigned to transfusion both intra- and postoperatively as demonstrated in the only relatively small-sized trial published by Bush et al.[30] where the randomization was abandoned in case of complicated intra- or postoperative course such as when there was evidence of ischaemia. Although several models were created to control for possible confounders, it is possible that some unmeasured variables might have influenced the results.

Conclusion

In the setting of major vascular surgery, RBT is associated with a significantly increased risk of 30-day death, myocardial infarction, or both. RBT was particularly harmful in patients without postoperative anaemia (haemoglobin $\geq$9.0 g/dL), with a fourfold increased risk of 30-day death, and we could not show significant protection even in patients with lower haemoglobin levels. Our findings caution against the use of RBT in stable patients after elective major vascular surgery especially if they have lesser degree of anaemia, and underscore the need for a specifically designed randomized trial.

Author contributions

F.B. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version of the manuscript.

Conflict of interest statement

All authors have no competing interests to declare.

Acknowledgements

We thank Dr Roberto D'Amico for statistical support and Professor Gioacchino Coppi, Dr Elisa Barbieri, and Dr Claudia Severino for data collection. *Funding/support*: Partly supported in by a grant from the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST). The funding sources for this study played no role in the design or conduct of the study, data management and analysis or manuscript preparation and review.

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